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(54) Title: ESTROGEN REPLACEMENT THERAPY

(57) Abstract: This invention relates to methods and pharmaceutical compositions for providing estrogen replacement therapy in perimenopausal, menopausal, and postmenopausal women through the continuous administration of conjugated estrogens.

ESTROGEN REPLACEMENT THERAPY

BACKGROUND

This invention relates to methods and pharmaceutical compositions for providing estrogen replacement therapy in perimenopausal, menopausal, and postmenopausal women through the continuous administration of conjugated estrogens.

Menopause is generally defined as the last natural menstrual period and is characterized by the cessation of ovarian function, leading to the substantial diminution of circulating estrogen in the bloodstream. Menopause is usually identified, in retrospect, after 12 months of amenorrhea. It is usually not a sudden event, but is often preceded by a time of irregular menstrual cycles prior to eventual cessation of menses. Following the cessation of menstruation, the decline in endogenous estrogen concentrations is typically rapid. There is a decrease in serum estrogens from circulating levels ranging from 40-250 pg/mL of estradiol and 40-170 pg/mL of estrone during ovulatory cycles to less than 15 pg/mL of estradiol and 30 pg/mL of estrone in postmenopausal women.

As these estrogens decline during the time preceding (perimenopause) and following the menopause (postmenopause), various physiological changes may result, including vulvar and vaginal atrophy causing vaginal dryness, pruritus and dyspareunia, and vasomotor instability manifested as hot flushes. Other menopausal disturbances may include depression, insomnia, and nervousness. The long-term physiologic effects of postmenopausal estrogen deprivation may result in significant morbidity and mortality due to increase in the risk factors for cardiovascular disease and osteoporosis. Menopausal changes in blood lipid levels, a major component of the pathogenesis of coronary heart disease (CHD), may be precursors to increased incidence of ischemic heart disease, atherosclerosis, and other cardiovascular disease. A rapid decrease in bone mass of both cortical (spine) and trabecular (hip) bone can be seen immediately after the menopause, with a total bone mass loss of 1% to 5% per year, continuing for 10 to 15 years.

Estrogen replacement therapy (ERT) is beneficial for symptomatic relief of hot flushes and genital atrophy and for prevention of postmenopausal osteoporosis. ERT has been recognized as an advantageous treatment for relief of vasomotor symptoms. There is no acceptable alternative to estrogen treatment for the atrophic changes in the vagina; estrogen therapy increases the vaginal mucosa and decreases vaginal dryness. Long term ERT is the key to preventing osteoporosis because it decreases bone loss, reduces spine and hip fracture, and prevents loss of height. In addition, ERT has been shown to be effective in increasing high density lipoprotein-cholesterol (HDL-C) and in reducing low density lipoprotein cholesterol (LDL-C), affording possible protection against CHD. ERT also can provide antioxidant protection against free radical mediated disorders or disease states. Estrogens have also been reported to confer neuroprotection, and inhibit neurodegenerative disorders, such as Alzheimer's disease (see U.S. Patent 5,554,601, which is hereby incorporated by reference). The following table contains a list of some of the estrogen preparations currently available in the US and Europe. Listings of such preparations are available in such as the Physicians' Desk Reference, The Orange Book, and the European equivalents thereof.

Estrogen replacement therapies available in the United States and/or Europe

Generic Name	Brand Name	Strength
Oral estrogens		
Conjugated equine estrogens (natural)	Premarin	0.3, 0.625, 0.9, 1.25, 2.5 mg
Conjugated estrogens (synthetic)	Cenestin	0.625, 0.9 mg
Esterified estrogens (75-80% estrone sulfate, 6-15% equilin sulfate derived from plant sterols)	Estratab	0.3, 0.625, 1.25, 2.5 mg
Estropipate (Piperazine estrone sulfate)	Ogen Ortho-Est	0.625, 1.25, 2.5 mg
Micronized estradiol	Estrace	0.5, 1.0, 2.0 mg
Raloxifene (SERM)	Evista	60 mg
Esterified estrogens and methylestosterone	Estratest	1.25 mg esterified estrogen and 2.5 mg methylestosterone
	Estratest HS	0.625 mg esterified estrogen and 1.25 mg methylestosterone
Estradiol valerate	Climaval	1 mg, 2 mg
Estradiol	Elleste Solo	1 mg, 2 mg
Estradiol	Estrofem	2 mg
Estradiol	Estrofem Forte	4 mg
Piperazine esterone sulfate	Harmogen	1.5 mg
Combination Product: Estrone Estradiol Estriol	Hormonin	1.4 mg 0.6 mg 0.27 mg
Estradiol valerate	Progynova	1 mg, 2 mg
Estradiol	Zumenon	1 mg, 2 mg
Transdermal estrogens		
Estradiol	Alora (twice wkly) Climara (weekly) Estraderm (2x wkly) Fem Patch (wkly) Vivelle (twice wkly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg of estradiol released daily (dose options for various products)
Estradiol	Dermestril	25, 50, 100 µg
Estradiol	Estraderm	25, 50, 100 µg
Estradiol	Evorel (Systen)	25, 50, 75, 100 µg
Estradiol	Fematrix	40, 80 µg
Estradiol	Menorest	25, 37.5, 50, 75 µg
Estradiol	Progynova TS And TS Forte (Climara)	50, 100 µg
Vaginal estrogens		
Conjugated equine estrogens	Premarin vaginal cream	0.625 mg/g
Dienestrol	Ortho dienestrol cream	0.1 mg/g
Estradiol	Estring	7.5 µg
Estropipate	Ogen vaginal cream	1.5 mg/g
Micronized estradiol	Estrace vaginal cream	1.0 mg/g

To minimize the occurrence of estrogen-related side effects and to maximize the benefit-risk ratio, the lowest dose effective in relief of symptoms and prevention of osteoporosis should be used. Although ERT reduces the relative risk (RR) for ischemic heart disease (RR, 0.50) and osteoporosis (RR, 0.40), the relative risk of endometrial cancer for postmenopausal women with a uterus may be increased. There are extensive clinical data showing that the relative risk of endometrial cancer can be reduced by the addition of a progestin, either sequentially or continuously. The addition of a progestin to estrogen therapy prevents estrogen-induced endometrial proliferation.

The addition of a progestin to ERT regimens, however, may ameliorate some of the favorable estrogen effects on lipids and may potentially impair glucose tolerance, it has desirably been an objective of HRT regimens to use the lowest dosage of progestin that will minimize or eliminate endometrial hyperplasia. It is therefore an object of this invention to provide low dosage ERT regimens that may minimize endometrial proliferation so that the need for concomitant progestin administration is diminished. Accordingly, the ERT regimens covered by this invention are particularly useful in treating perimenopausal, menopausal, or postmenopausal women when accompanied by adequate physician monitoring, and are also particularly useful in treating subgroups of hysterectomized or progestin intolerant women.

DESCRIPTION OF THE INVENTION

The purpose of this invention is to provide the significant benefits of a commercially successful ERT product, such as PREMARIN (0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg, or 2.5 mg conjugated equine estrogens, USP), while lowering the dosage of conjugated estrogens below that which has previously been demonstrated to be effective. This invention provides a method of treating or inhibiting menopausal or postmenopausal disorders in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises providing to said woman, continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens (natural or synthetic). The dosage is preferably provided as a pharmaceutical composition for use in treating menopausal or

postmenopausal disorders. This invention further provides a pharmaceutical pack containing the daily dosage units of conjugated estrogen.

Conjugated estrogens refer to estrogenic steroidal substances in which one or more functional groups (typically hydroxyl groups) on the steroid exists as a conjugate (typically a sulfate or glucuronide). The conjugated estrogens may be a single conjugated estrogen, or may consist of mixtures of various conjugated estrogens. Numerous conjugated estrogens are described in the literature or are commercially available that are capable of being formulated for use in this invention either as a unitary estrogen, or may be mixed together with other synthetic and/or natural estrogens.

Conjugated estrogens may also contain other steroidal or non-steroidal compounds, which may, or may not, contribute to the overall biological effect. Such compounds include, but are not limited to, unconjugated estrogens, androstanes, and pregnanes. Preferred conjugated estrogens for use in this invention are PREMARIN (conjugated equine estrogens, USP, conforming with the monograph for conjugated estrogens in USP25) and CENESTIN (synthetic conjugated estrogens, A).

PREMARIN (conjugated estrogens tablets, USP) for oral administration contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate, and at least the following 8 concomitant components, also as sodium sulfate conjugates: 17α-dihydroequilin, 17α-estradiol, Δ8,9-dehydroestrone, 17β-dihydroequilin, 17β-estradiol, equilenin, 17α-dihydroequilenin, and 17β-dihydroequilenin. PREMARIN is indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause; treatment of vulvar and vaginal atrophy; and prevention of osteoporosis, as well as other indications approved for estrogen products.

CENESTIN (synthetic conjugated estrogens, A) tablets for oral administration contain a blend of 9 synthetic estrogenic substances: sodium estrone sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium equilenin sulfate, sodium 17α-dihydroequilenin sulfate, sodium equilin sulfate, sodium 17β-dihydro-equilin sulfate, sodium 17β-estradiol sulfate, sodium 17α-dihydroequilenin sulfate.

CENESTIN is indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause.

PREMARIN and CENESTIN are available from commercial sources (Wyeth-Ayerst - PREMARIN; Duramed - CENESTIN).

It is preferred that the conjugated estrogen constituent is PREMARIN. It is preferred that the dosage of PREMARIN is from about 0.25 mg per day to about 0.1 mg per day, and is more preferred that the dosage of PREMARIN is from about 0.2 mg per day to about 0.1 mg per day, with a daily dosage of about 0.2 mg being specifically preferred. It is also preferred that the ERT regimens described herein be administered to hysterectomized women, or women with an uterus accompanied by careful physician monitoring for endometrial hyperplasia.

If desired, the conjugated estrogen regimens of this invention can be administered in conjunction with a progestin, particularly medroxyprogesterone acetate (MPA, commercially available from Wyeth-Ayerst). When MPA is used as the progestin, it is preferred that the daily dosage of MPA is 2.5 mg or less. Such concomitant administration can be as a combination (as defined below), or that the progestin can be provided for only part of the treatment period. For example, PREMARIN may administered for 28-days per 28-day treatment period, and MPA may be administered on days 15-28 of the same 28-day treatment period.

As used in accordance with this invention, the term "menopausal or postmenopausal disorder" refers to conditions, disorders, or disease states that are at least partially caused by the decreased estrogen production occurring during the perimenopausal, menopausal, or post-menopausal stages of a woman's life. Such disorders typically include, but are not limited to, one or more of, vaginal and vulvar atrophy, vasomotor instability, urinary incontinence, and increased risk of developing osteoporosis, cardiovascular disease, and diseases related to the oxidative damage from free radicals. As used herein, menopausal also includes conditions of decreased estrogen production that may be surgically, chemically, or be caused by a disease state which leads to premature diminution or cessation of ovarian function.

The term "daily" means that the dosage is to be administered at least once daily. The frequency is preferred to be once daily, but may be more than once daily, provided that any specified daily dosage is not exceeded.

The term "continuous and uninterrupted" means that there is no break in the treatment regimen, during the treatment period. Thus, "continuous, uninterrupted administration" of a combination, means that the combination is administered at least once daily during the entire treatment period. It is expected that the treatment period for the ERT regimens of this invention will be for at least 30 days, preferably 120 days, and most preferably as long term treatment, and possibly indefinite, as one of the primary reasons for administering ERT is to treat or inhibit menopausal or postmenopausal disorders. Treatment periods also may vary depending on the symptoms to be treated. For example, for the treatment of vasomotor symptoms, it is preferred that the treatment may last from one month to several years, depending on the severity and duration of the symptoms. Physician evaluation along with patient interaction will assist the determination of the duration of treatment. For the treatment or inhibition of osteoporosis, it is preferred that the treatment period could last from six months to a number of years, or indefinitely.

This invention, also covers short term treatments or treatments of a finite term, that may be less than the 30 day preferred treatment period. It is anticipated that a patient may miss, or forget to take, one or a few dosages during the course of a treatment regimen, however, such patient is still considered to be receiving continuous, uninterrupted administration.

The term "fixed daily dosage" means that the same dosage is given every day during the treatment period. One aspect of this invention also covers situations in which a fixed daily dosage of the ERT regimen is not given every day during the treatment period. For example, the dosage of a patient may need to be adjusted (either up or down), to achieve the desired effect during the middle of a treatment period.

The term "providing," with respect to providing a dosage of one or both of the components of this invention, means either directly administering such a component of this invention, or administering a prodrug, derivative, or analog which will form the equivalent amount of the component within the body.

It is preferred that the conjugated estrogens of this invention are provided orally. The specific dosages of conjugated estrogens plus MPA combinations of this invention that are disclosed herein are oral dosages.

The term "combination" means that the daily dosage of each of the components of the combination is administered during the treatment day. The

components of the combination are preferably administered at the same time; either as a unitary dosage form containing both components, or as separate dosage units; the components of the combination can be administered at different times during the day, provided that the desired daily dosage is achieved.

In accordance with this invention, continuously and uninterruptedly providing a daily dosage from about 0.25 mg to about 0.1 mg conjugated estrogens is useful in treating or inhibiting menopausal or postmenopausal disorders in perimenopausal, menopausal, or postmenopausal women. More particularly, the combinations described herein are useful in treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections; vasomotor symptoms, including hot flushes, myalgia, arthralgia, insomnia, irritability, and the like; inhibiting or retarding bone demineralization; increasing bone mineral density; and treating or inhibiting osteoporosis.

The combinations of this invention also exert a cardioprotective effect in perimenopausal, menopausal, and postmenopausal women, and are therefore useful in lowering cholesterol, Lp(a), and LDL levels; inhibiting or treating hypercholesteremia; hyperlipidemia; cardiovascular disease; atherosclerosis; peripheral vascular disease; restenosis, and vasospasm; and inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage.

The combinations of this invention are antioxidants, and are therefore useful in inhibiting disorders or disease states which involve free radicals. More particularly, the combinations of this invention are useful in treating or inhibiting free radical involvement in the development of cancers, central nervous system disorders, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, amyotrophic lateral sclerosis, aging effects, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures.

The combinations of this invention are useful in treating or inhibiting dementias, neurodegenerative disorders, and Alzheimer's disease; providing neuroprotection or cognition enhancement.

Conjugated estrogens may be formulated neat or may be combined with one or more pharmaceutically acceptable carriers for administration. For example, solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

In the Physicians' Desk Reference, PREMARIN is described as containing calcium phosphate tribasic, calcium sulfate, carnuaba wax, cellulose, glyceryl momooleate, lactose, magneseum stearate, methyl cellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, and titanium dioxide as inactive ingredients. This would be a typical formulation for PREMARIN.

CENESTIN is described as containing ethylcellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate as inactive ingredients. Formulations covering CENESTIN are described in US Patent 5,908,638, which is hereby incorporated by reference. This would be a typical formulation for CENESTIN.

Conjugated estrogens may be formulated in a core containing the conjugated estrogens, and several components including alcohol, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, and starch. The core can be covered with a coating made from components such as ethylcellulose, and triethyl citrate. Conjugated estrogens can be incorporated in granules, spheroids or other multiparticulate forms, and, if necessary, coated to provide adequate stability.

This invention also provides a pharmaceutical pack, containing any number of daily pharmaceutical dosage units. Preferably, and conventionally, the pack contains 28 tablets or multiples thereof. The pack should indicate that the dosage units are to be taken consecutively on a daily basis until the treatment period has ended, or until the pack has been completed. The next pack should be started on the next consecutive day.

The ERT regimens described in this invention may also be administered as a transdermal patch or as a vaginal cream. For example, PREMARIN vaginal cream containing 0.625 mg conjugated equine estrogens, USP, is formulated to contain USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil as excipients. ERT regimens covered by this invention can be formulated similarly.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

CLAIMS

1. A method of treating or inhibiting menopausal or postmenopausal disorders in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

2. The method according to claim 1, wherein the conjugated estrogens is conjugated equine estrogens, USP.

3. The method according to claim 2, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

4. The method according to claim 3, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

5. The method according to claim 1, wherein the conjugated estrogens is synthetic conjugated estrogens, A.

6. A method of treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

7. The method according to claim 6, wherein the conjugated estrogens is conjugated equine estrogens, USP.

8. The method according to claim 7, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

9. The method according to claim 8, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

10. The method according to claim 6, wherein the vasomotor symptom is hot flushes.

11. The method according to claim 6, wherein the conjugated estrogens is synthetic conjugated estrogens, A.

12. A method of inhibiting or retarding bone demineralization or treating or inhibiting osteoporosis in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

13. The method according to claim 12, wherein the conjugated estrogens is conjugated equine estrogens, USP.

14. The method according to claim 13, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

15. The method according to claim 14, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

16. A method of treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

17. The method according to claim 16, wherein the conjugated estrogens is conjugated equine estrogens, USP.

18. The method according to claim 17, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

19. The method according to claim 18, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

20. A method of lowering cholesterol, Lp(a), or LDL levels; inhibiting or treating hypercholesteremia; hyperlipidemia; cardiovascular disease; atherosclerosis; peripheral vascular disease; restenosis, vasospasm; or inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage, in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

21. The method according to claim 20, wherein the conjugated estrogens is conjugated equine estrogens, USP.

22. The method according to claim 21, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

23. The method according to claim 22, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

24. A method of treating or inhibiting free radical involvement in the development of cancers, central nervous system disorders, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, amyotrophic lateral sclerosis, aging effects, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

25. The method according to claim 24, wherein the conjugated estrogens is conjugated equine estrogens, USP.

26. The method according to claim 25, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

27. The method according to claim 26, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

28. A method of treating or inhibiting dementias, neurodegenerative disorders, and Alzheimer's disease; providing neuroprotection or cognition enhancement in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

29. The method according to claim 28, wherein the conjugated estrogens is conjugated equine estrogens, USP.

30. The method according to claim 31, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

31. The method according to claim 30, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

32. A pharmaceutical composition for use in treating menopausal or postmenopausal disorders, which comprises dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens, and a pharmaceutical carrier.

33. The composition according to claim 32, wherein the conjugated estrogens is conjugated equine estrogens, USP.

34. The composition according to claim 33, wherein the dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

35. The composition according to claim 34, wherein the dosage of conjugated equine estrogens, USP is about 0.2 mg.

36. A pharmaceutical dosage unit which comprises conjugated estrogens, a dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens and a pharmaceutical carrier.

37. The dosage unit according to claim 36, wherein the conjugated estrogens is conjugated equine estrogens, USP.

38. The dosage unit according to claim 37, wherein the dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

39. The dosage unit according to claim 38, wherein the dosage of conjugated equine estrogens, USP is about 0.2 mg.

40. A method of minimizing or reducing levels of breast pain in a woman receiving hormone replacement therapy, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

41. The method according to claim 40, wherein the conjugated estrogens is conjugated equine estrogens, USP.

42. The method according to claim 41, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

43. The method according to claim 42, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

44. A method of minimizing spotting or breakthrough bleeding; or achieving amenorrhea in a woman receiving hormone replacement therapy, which comprises

orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg.

45. The method according to claim 44, wherein the conjugated estrogens is conjugated equine estrogens, USP.

46. The method according to claim 45, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

47. The method according to claim 46, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

48. A method of increasing bone mineral density in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from about 0.25 mg to about 0.1 mg conjugated estrogens.

49. The method according to claim 48, wherein the conjugated estrogens is conjugated equine estrogens, USP.

50. The method according to claim 49, wherein the daily dosage of conjugated equine estrogens is from about 0.2 mg to about 0.1 mg.

51. The method according to claim 50, wherein the daily dosage of conjugated equine estrogens, USP is about 0.2 mg.

52. A pharmaceutical pack for use in the treatment of menopausal or postmenopausal disorders comprising a plurality of pharmaceutical dosage units as defined in any of claims 36 to 39 for continuous uninterrupted daily administration of a daily dosage

53. Use of conjugated estrogens in the manufacture of a pharmaceutical composition as defined in any of claims 32 to 35 or one or more pharmaceutical

dosage units as defined in any of claims 36 to 39, for the treatment of menopausal or post-menopausal disorders.

54. Use of conjugated estrogens in the manufacture of a pharmaceutical pack as defined in claim 52, for the treatment of menopausal or post-menopausal disorders.

55. Use of conjugated estrogens according to claim 52 or 53 for the treatment or inhibition of vasomotor symptoms in a perimenopausal, menopausal or postmenopausal woman in need thereof.

56. Use of conjugated estrogens according to claim 55 wherein the vasomotor symptom is hot flushes.

57. Use of conjugated estrogens according to claim 52 or 53 for inhibiting or retarding bone demineralization or treating or inhibiting osteoporosis in a perimenopausal, menopausal, or postmenopausal woman in need thereof.

58. Use of conjugated estrogens according to claim 52 or 53 for treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections in a perimenopausal, menopausal, or postmenopausal woman in need thereof.

59. Use of conjugated estrogens according to claim 52 or 53 for lowering cholesterol, Lp(a), or LDL levels; inhibiting or treating hypercholesteremia; hyperlipidemia; cardiovascular disease; atherosclerosis; peripheral vascular disease; restenosis, vasospasm; or inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage, in a perimenopausal, menopausal, or postmenopausal woman in need thereof

60. Use of conjugated estrogens according to claim 52 or 53 for treating or inhibiting free radical involvement in the development of cancers, central nervous system disorders, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active

hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, amyotrophic lateral sclerosis, aging effects, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures in a perimenopausal, menopausal, or postmenopausal woman in need thereof

61. Use of conjugated estrogens according to claim 52 or 53 for treating or inhibiting dementias, neurodegenerative disorders, and Alzheimer's disease; providing neuroprotection or cognition enhancement in a perimenopausal, menopausal, or postmenopausal woman in need thereof

62 Use of conjugated estrogens according to claim 52 or 53 for minimizing or reducing levels of breast pain in a woman receiving hormone replacement therapy.

63. Use of conjugated estrogens according to claim 52 or 53 for minimizing spotting or breakthrough bleeding; or achieving amenorrhea in a woman receiving hormone replacement therapy.

64. Use of conjugated estrogens according to claim 52 or 53 for increasing bone mineral density in a perimenopausal, menopausal, or postmenopausal woman in need thereof

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant: WYETH [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

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Published:
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(88) Date of publication of the international search report:
9 October 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ESTROGEN REPLACEMENT THERAPY

(57) Abstract: This invention relates to methods and pharmaceutical compositions for providing estrogen replacement therapy in perimenopausal, menopausal, and postmenopausal women through the continuous administration of conjugated estrogens.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565 A61K31/566 A61K31/567 A61P15/12 A61P5/30
A61P19/10 A61P15/02 A61P13/02 A61P3/06 A61P9/00
A61P9/10 A61P9/14 A61P39/06 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 13538 A (CHIESI FARMA SPA) 20 August 1992 (1992-08-20)	1-3,6-8, 10, 12-14, 24-26, 32-34, 36-38, 48-50, 52-57, 60,64
A	page 2, line 2 - line 9 page 2, line 31 -page 3, line 6 page 4, line 24 -page 6, line 11 page 8, line 1 -page 10, line 24 table 2 example 1 page 12, line 27 -page 13, line 1 page 13, line 27 -page 14, line 3 claims 1,2,4 -/--	40-47, 62,63

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2003	26. 06. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Cielen, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 22457 A (UNIV CALIFORNIA ;MORRIS R CURTIS JR (US); SEBASTIAN ANTHONY (US)) 13 October 1994 (1994-10-13)	1-4, 12-15, 24-27, 32-39, 48-53, 57,60,64
A	page 1, line 14 - line 20 page 2, line 23 -page 3, line 35 page 4, line 26 -page 5, line 28 page 6, line 1 - line 8 page 9, line 16 - line 25 page 11, line 21 - line 33 page 12, line 16 - line 38 example I claims 1,9	40-47, 62,63
X	US 3 608 075 A (GAHWYLER MAX ET AL) 21 September 1971 (1971-09-21)	1,6,10, 16,32, 36, 52-56,58
A	abstract column 1, line 1 - line 26 column 2, line 15 -column 3, line 11 examples 2,10,12 claims 1-5,7,8	40-47, 62,63
X	EP 0 322 020 A (AKZO NV) 28 June 1989 (1989-06-28) the whole document	1,12,24, 32,36, 48, 52-54, 57,60,64
X	WO 99 59969 A (AMERICAN HOME PROD) 25 November 1999 (1999-11-25) page 3, line 19 -page 4, line 3 page 6, line 28 -page 8, line 14 page 9, line 18 -page 10, line 14 page 11, line 16 - line 26 page 13, line 30 -page 14, line 2 claims 23,25	1-3, 12-14, 24-26, 32-34, 36-38, 44-46, 48-50, 52-54, 57,60, 63,64

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/07971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GEOLA F L ET AL: "BIOLOGICAL EFFECTS OF VARIOUS DOSES OF CONJUGATED EQUINE ESTROGENS IN POST MENOPAUSAL WOMEN" JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 51, no. 3, 1980, pages 620-625, XP001131919 ISSN: 0021-972X abstract page 620, column 1, paragraph 1 -column 2, paragraph 1 page 621, column 1, paragraph 1 page 622, column 2, paragraph 4 -page 623, column 1, paragraph 1 ---	32-34, 36-38,52
X	US 3 639 599 A (IRMSCHER KLAUS ET AL) 1 February 1972 (1972-02-01) column 1, line 30 - line 52 column 3, line 22 - line 29 column 3, line 63 - line 72 column 5, line 33 - line 36 claims 1,6 ---	1,6,10, 12,24, 32,36, 48, 52-57, 60,64
X	US 4 154 820 A (SIMOONS JOHAN R A) 15 May 1979 (1979-05-15) abstract column 4, line 26 - line 43 column 5, line 5 - line 16 column 6, line 12 - line 23 claims 1,2,4,7,8 ---	1,5,32, 36,44, 52-54,63
X	DE 43 26 948 C (UMBREIT KLAUS DR MED) 17 November 1994 (1994-11-17)	32-39,52
A	column 2, line 47 -column 3, line 8 column 3, line 34 - line 41 ---	24-27,60
X	EP 0 722 720 A (AMERICAN HOME PROD) 24 July 1996 (1996-07-24)	32-39
A	page 2, line 37 -page 3, line 6 page 6, line 22 - line 28 claims 8-11 --- -/--	52

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/07971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 4 980 358 A (SMITH R ARNOLD) 25 December 1990 (1990-12-25) column 1, line 46 -column 2, line 20 column 2, line 48 - line 55 column 4, line 21 - line 25 examples 1-4,7 column 6, line 20 - line 45 column 8, line 1 - line 15 claims 1,3,4	32-43, 52,62 1-4, 16-19, 24-27, 53,54, 58,60
X	WO 94 09789 A (AMERICAN HOME PROD ;UNIV WAKE FOREST (US)) 11 May 1994 (1994-05-11) page 1, line 3 - line 8 page 3, line 30 -page 6, line 3 table 1 page 9, line 8 - line 9 page 10, line 1 - line 26 claims 1,3,4,6,13,15,17,20-23	1,20,24, 32,36, 52-54, 59,60
X	WO 98 50414 A (AMERICAN HOME PROD) 12 November 1998 (1998-11-12) page 2, line 20 -page 4, line 21 page 14, line 7 - line 30 page 15, line 24 - line 25 page 16, line 9 - line 21 claims 5-9	1,6,10, 16,20, 24,32, 36,48, 52-60,64
X	WO 98 45315 A (AMERICAN HOME PROD) 15 October 1998 (1998-10-15) page 1, line 19 - line 33 page 10, line 11 -page 11, line 27 page 12, line 26 - line 27 page 13, line 9 - line 18 claims 9-22 -/--	1,6,10, 11,16, 20,24, 28,32, 36,48, 52-61,64

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International Application No
PCT/US 02/07971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 50413 A (AMERICAN HOME PROD) 12 November 1998 (1998-11-12) page 1, line 19 - line 30 page 2, line 12 - line 20 page 6, line 1 - line 26 page 7, line 24 - line 25 page 8, line 6 - line 15 claims 10-16,21	1,6,10, 11,16, 20,24, 28,32, 36,48, 52-61,64
X	WO 98 16544 A (AMERICAN HOME PROD) 23 April 1998 (1998-04-23) page 1, line 6 -page 2, line 15 page 9, line 11 - line 34 page 11, line 1 - line 2 page 11, line 24 - line 32 claims 9-23	1,6,10, 11,16, 20,24, 28,32, 36,48, 52-61,64
X	WO 99 12531 A (HESCH ROLF DIETER) 18 March 1999 (1999-03-18) page 3, paragraph 4 -page 4, paragraph 2 page 4, paragraph 5 page 5, paragraphs 1,6 page 6, paragraphs 1,2,7 page 8, paragraph 3 page 8, paragraph 5 -page 9, paragraph 1 page 10, paragraph 1 - paragraph 2 page 11, paragraph 4 -page 12, paragraph 2 claims 1,3,8,10,11,16,18	24,44, 60,63
X	WO 01 00215 A (NOTELOVITZ MORRIS ;UNIV WAKE FOREST (US)) 4 January 2001 (2001-01-04) page 6, line 10 - line 12 page 13, line 14 -page 14, line 2 page 14, line 28 -page 15, line 6 page 15, line 28 - line 29 page 17, line 5 - line 6 page 18, line 12 - line 32 claims 11,12,16,17,19	1-4, 24-31, 60,61

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PCT/US 02/07971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	ARCHER D F ET AL: "Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate." OBSTETRICS & GYNECOLOGY, vol. 83, no. 5, 1994, pages 686-692, XP008018152 ISSN: 0029-7844 abstract tables 3-5 page 689, column 2, paragraph 2 page 692, column 1, paragraph 2 ---	44,63
A	PARFITT K.: "Martindale - The complete drug reference - Thirthy-second edition" , PHARMACEUTIACL PRESS , LONDON UK XP002226921 page 1437, column 3 -page 1438, column 3 page 1457, column 3 -page 1458, column 1 ---	1-27, 48-51, 53-61,64
A	BEERS, M. AND BERKOW R.: "The Merck Manual of Diagnosis and Therapy - Seventeenth Edition" , MERCK RESEARCH LABORATORIES , WHITEHOUSE STATION, N.J. XP002226922 page 1942, column 2, paragraph 4 -page 1944, column 1, paragraph 1 ---	1-27, 48-51, 53-60,64
A	CHEANG A ET AL: "A risk-benefit appraisal of transdermal estradiol therapy." DRUG SAFETY: AN INTERNATIONAL JOURNAL OF MEDICAL TOXICOLOGY AND DRUG EXPERIENCE. NEW ZEALAND NOV 1993, vol. 9, no. 5, November 1993 (1993-11), pages 365-379, XP008018150 ISSN: 0114-5916 abstract page 374, column 1, paragraph 2 table III page 376, column 1, paragraph 4 ---	40-47, 62,63
A	MAGOS A L ET AL: "AMENORRHEA AND ENDOMETRIAL ATROPHY WITH CONTINUOUS ORAL ESTROGEN AND PROGESTOGEN THERAPY IN POSTMENOPAUSAL WOMEN" OBSTETRICS AND GYNECOLOGY, vol. 65, no. 4, 1985, pages 496-499, XP008018151 ISSN: 0029-7844 abstract page 496, column 2, paragraph 3 page 497, column 1, paragraph 4 -column 2, paragraph 1 page 498, column 2, paragraph 3 ---	44-47,63

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ETTINGER B.: "Personal perspective on low-dose estrogen therpay for postmenopausal women." MENOPAUSE, vol. 6, 1999, pages 273-276, XP008018271 the whole document	40-47, 62,63
A	MCNICHOLAS M.M.J. ET AL: "Pain and increased mammographic density in women receiving hormone replacement therapy: A prospective study." AMERICAN JOURNAL OF ROENTGENOLOGY, (1994) 163/2 (311-315). , XP008018224 abstract page 314, column 2, paragraph 2 -page 315, column 1, paragraph 1	40-43,62
A	ROMER W ET AL: "Novel @?scavestrogens@? and their radical scavenging effects, iron-chelating, and total antioxidative activities: DELTA-dehydro derivatives of 17alpha-estradiol and 17beta-estradiol" STEROIDS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 62, no. 3, 1 March 1997 (1997-03-01), pages 304-310, XP004057109 ISSN: 0039-128X page 604, column 2, paragraph 1	24,60
P,X	WO 01 35106 A (GANDY SAM ;FRAIL DONALD E (US); AMERICAN HOME PROD (US); PETANESCA) 17 May 2001 (2001-05-17) page 4, line 20 -page 5, line 1 page 5, line 29 -page 6, line 3 page 8, line 25 - line 27 page 12, line 21 - line 26 page 17, line 10 - line 15 page 18, line 16 - line 24 page 19, line 15 - line 30 page 20, line 12 - line 15 page 27, line 26 -page 28, line 2 claims 1,4,7,8,13,20,22,24	1,24,28, 60,61
E	WO 02 074292 A (WYETH) 26 September 2002 (2002-09-26) the whole document	1-64

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International Application No
PCT/US 02/07971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 058706 A (ENDEAVOR PHARMACEUTICALS ;LEONARD THOMAS W (US); WALDON R FORREST) 1 August 2002 (2002-08-01) page 2, paragraph 9 -page 3, paragraph 17 page 4, paragraph 20 page 11, paragraph 49 claims 1,2,5,6,14,17,18,21,22,25,26	1,2,32, 33,36, 37,52-54

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/07971

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-31, 40-51, 55-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-23, 28-39, 48-59, 61, 64

A method of treating or inhibiting menopausal or postmenopausal disorders in a perimenopausal, menopausal or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from 0.1 mg to 0.25 mg conjugated estrogens. Pharmaceutical compositions or dosage units comprising 0.1 mg to 0.25 mg conjugated estrogens, and pharmaceutical packs containing a plurality of such dosage units.

2. Claims: 24-27, 60

A method of treating or inhibiting free radical involvement in the development of cancers, central nervous system disorders, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, amyotrophic lateral sclerosis, aging effects, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures in a perimenopausal, menopausal or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from 0.1 mg to 0.25 mg conjugated estrogens.

3. Claims: 40-47, 62, 63

A method of minimizing levels of breast pain or spotting or breakthrough bleeding, or achieving amenorrhea in a woman receiving hormone replacement therapy, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a daily dosage in an amount from 0.1 mg to 0.25 mg conjugated estrogens.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 6, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52-64 relate to a very large number of possible compounds, namely "conjugated estrogens". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Moreover, present claims 1-9, 11, 20-31, 53-55 and 59-61 relate to diseases which actually are not well-defined. The use of the definitions "menopausal or postmenopausal disorders", "vasomotor symptoms", "inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage", "inhibiting free radical involvement", "central nervous system disorders", "bone disease", "inflammatory disorders", "autoimmune diseases", "neurodegenerative disorders" and "providing neuroprotection" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the conjugated estrogens specifically disclosed in the claims and the description, namely conjugated equine estrogens, USP and synthetic conjugated estrogens, A, and their use in the treatment of the diseases specifically mentioned in the claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/07971

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9213538	A	20-08-1992	IT	1244697 B	08-08-1994
			AU	1188492 A	07-09-1992
			CA	2101547 A1	02-08-1992
			WO	9213538 A1	20-08-1992
			EP	0569415 A1	18-11-1993
			HU	64848 A2	28-03-1994
			IE	920219 A1	12-08-1992
			NZ	241418 A	26-03-1993
			ZA	9200661 A	28-10-1992
WO 9422457	A	13-10-1994	AU	692155 B2	04-06-1998
			AU	6621994 A	24-10-1994
			BR	9406101 A	19-12-1995
			CA	2159354 A1	13-10-1994
			CN	1120314 A	10-04-1996
			EP	0692965 A1	24-01-1996
			JP	8508502 T	10-09-1996
			WO	9422457 A1	13-10-1994
US 3608075	A	21-09-1971	NONE		
EP 0322020	A	28-06-1989	AU	2690888 A	22-06-1989
			CN	1036328 A	18-10-1989
			DK	700588 A	23-06-1989
			EP	0322020 A1	28-06-1989
			JP	1211527 A	24-08-1989
			ZA	8809357 A	27-12-1989
WO 9959969	A	25-11-1999	AU	3894299 A	06-12-1999
			CA	2331318 A1	25-11-1999
			CN	1309637 T	22-08-2001
			EP	1080073 A1	07-03-2001
			JP	2002515484 T	28-05-2002
			WO	9959969 A1	25-11-1999
US 3639599	A	01-02-1972	BE	722511 A	18-04-1969
			DK	120812 B	19-07-1971
			ES	359336 A1	01-07-1970
			FR	7983 M	08-06-1970
			GB	1175468 A	23-12-1969
			IL	30594 A	30-05-1972
			SE	365408 B	28-03-1974
US 4154820	A	15-05-1979	NONE		
DE 4326948	C	17-11-1994	DE	4326948 C1	17-11-1994
EP 0722720	A	24-07-1996	US	5547948 A	20-08-1996
			AT	185482 T	15-10-1999
			AU	705879 B2	03-06-1999
			AU	4098296 A	25-07-1996
			BR	9600100 A	27-01-1998
			CA	2167254 A1	18-07-1996
			CN	1141168 A ,B	29-01-1997
			CZ	9600128 A3	14-08-1996
			DE	69604600 D1	18-11-1999
			DE	69604600 T2	24-02-2000
			DK	722720 T3	03-01-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/07971

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0722720 A		EE	9600002 A	15-08-1996
		EP	0722720 A1	24-07-1996
		ES	2137627 T3	16-12-1999
		FI	960210 A	18-07-1996
		GR	3031920 T3	31-03-2000
		HK	1009935 A1	19-05-2000
		HU	9600090 A2	30-12-1996
		IL	116772 A	17-08-1999
		JP	8231436 A	10-09-1996
		NO	960191 A	18-07-1996
		NZ	280826 A	20-12-1996
		PL	312336 A1	22-07-1996
		RU	2152207 C1	10-07-2000
		SG	33663 A1	18-10-1996
		SI	722720 T1	31-12-1999
		SK	4996 A3	09-04-1997
		TR	960713 A2	21-08-1996
		TW	460301 B	21-10-2001
		US	5759576 A	02-06-1998
		US	5759577 A	02-06-1998
		ZA	9600301 A	15-07-1997
US 4980358 A	25-12-1990	US	4929640 A	29-05-1990
		WO	8909599 A1	19-10-1989
		US	5073555 A	17-12-1991
WO 9409789 A	11-05-1994	AT	204755 T	15-09-2001
		AU	5544994 A	24-05-1994
		CA	2148357 A1	11-05-1994
		CN	1094283 A ,B	02-11-1994
		DE	69330680 D1	04-10-2001
		DE	69330680 T2	13-06-2002
		DK	666747 T3	27-12-2001
		EP	0666747 A1	16-08-1995
		ES	2161750 T3	16-12-2001
		JP	8503702 T	23-04-1996
		PT	666747 T	28-02-2002
		SG	49785 A1	15-06-1998
		WO	9409789 A1	11-05-1994
		US	5510342 A	23-04-1996
		ZA	9308016 A	28-04-1995
WO 9850414 A	12-11-1998	AT	230756 T	15-01-2003
		AU	750306 B2	18-07-2002
		AU	7261198 A	27-11-1998
		BR	9809592 A	04-07-2000
		CN	1255142 T	31-05-2000
		DE	69810617 D1	13-02-2003
		DK	983294 T3	24-02-2003
		EP	0983294 A1	08-03-2000
		JP	2001526654 T	18-12-2001
		TW	464653 B	21-11-2001
		WO	9850414 A1	12-11-1998
		ZA	9803729 A	04-11-1999
WO 9845315 A	15-10-1998	AU	738486 B2	20-09-2001
		AU	6946298 A	30-10-1998
		BR	9809748 A	20-06-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/07971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9845315 A		CN 1259137 T	05-07-2000
		EP 0973790 A1	26-01-2000
		JP 2001518896 T	16-10-2001
		NZ 500217 A	30-11-2001
		WO 9845315 A1	15-10-1998
		ZA 9802913 A	06-10-1999
WO 9850413 A	12-11-1998	AT 230413 T	15-01-2003
		AU 730300 B2	01-03-2001
		AU 7165598 A	27-11-1998
		BR 9809437 A	13-06-2000
		CN 1254341 T	24-05-2000
		DE 69810461 D1	06-02-2003
		DK 980383 T3	14-04-2003
		EP 0980383 A1	23-02-2000
		JP 2001523266 T	20-11-2001
		WO 9850413 A1	12-11-1998
		ZA 9803698 A	01-11-1999
WO 9816544 A	23-04-1998	AU 743530 B2	31-01-2002
		AU 5145998 A	11-05-1998
		BR 9712628 A	26-10-1999
		CN 1239967 A	29-12-1999
		EP 0934334 A1	11-08-1999
		HU 9903369 A2	28-06-2001
		JP 2001502328 T	20-02-2001
		KR 2000049055 A	25-07-2000
		NZ 335183 A	29-09-2000
		WO 9816544 A1	23-04-1998
		ZA 9709069 A	09-04-1999
WO 9912531 A	18-03-1999	DE 19739916 A1	18-03-1999
		AU 1140999 A	29-03-1999
		WO 9912531 A2	18-03-1999
		EP 1310257 A2	14-05-2003
		EP 1011682 A2	28-06-2000
		US 2003073673 A1	17-04-2003
		US 6500814 B1	31-12-2002
WO 0100215 A	04-01-2001	AU 6053900 A	31-01-2001
		WO 0100215 A1	04-01-2001
		US 6524616 B1	25-02-2003
WO 0135106 A	17-05-2001	AU 1459201 A	06-06-2001
		CA 2390161 A1	17-05-2001
		EP 1272853 A2	08-01-2003
		WO 0135106 A2	17-05-2001
WO 02074292 A	26-09-2002	WO 02074292 A2	26-09-2002
		US 2002169150 A1	14-11-2002
WO 02058706 A	01-08-2002	WO 02058706 A2	01-08-2002
		US 2002151530 A1	17-10-2002